Animal &
Plant Health
Agency

Risk assessment for the use of *Mycobacterium bovis* BCG Danish Strain 1331 in cattle: risks to public health

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Introduction

- In order to gain approval from the UK Veterinary Medicines Directorate (VMD) for a new Marketing Authorisation (MA) for CattleBCG a quantitative risk assessment is required.

- AIM: assess the risks to public health due to the possibility of CattleBCG being present in the food chain and, in particular, within milk and beef products.

- Start date: 1st October 2013
- Risk assessment completed: 28th August 2014

Risk questions

- What is the risk of human illness with CattleBCG due to the consumption of a typical serving of milk and milk products?

- What is the risk of human illness with CattleBCG due to the consumption of a typical serving of beef products?

Summary of risk assessments

Product	Unpasteurised/ Pasteurised	Qualitative	Quantitative
Milk	Unpasteurised	✓	✓
	Pasteurised	✓	
Cheese	Unpasteurised Hard	✓	(✓)
	Unpasteurised Semi-hard/soft	✓	(✓)
Beef	Mince	✓	(✓)
	Offal	✗	✗

(✓) denotes a full quantitative risk assessment was not developed

Qualitative methods

- **Risk Nomenclature (EFSA 2006)**
  - **Negligible** – Risk or frequency/consequence is so low as to not merit consideration.
  - **Very Low** – Risk or frequency/consequence is almost negligible, but due to uncertainty or other extenuating circumstances cannot be excluded from consideration.
  - **Low** – Risk or frequency/consequence is small/infrequent, but still worth considering intervention/mitigation.
  - **Medium** – Occurs frequently, or event associated with a modest consequence.
  - **High** – Event occurs often, and/or is associated with a significant consequence.
  - **Very High** – Event occurs almost certainly, and/or is associated with a serious consequence.

Quantitative methods

- Deterministic models
  - Lack of data / uncertainty does not warrant stochastic models.
  - Comparison between products is qualitative.
- Different approaches for milk and beef products.
- Scenario analyses
  - Probability of illness if the scenario occurs
  - Probability of scenario occurring.

Risk framework

- Release: Probability and concentration of the release of CattleBCG
- Exposure: Probability and concentration of human exposure to CattleBCG
- Consequence: Potential consequences of a given exposure to CattleBCG (Dose-response relationship)
- Risk estimate: Integrates the results of the above assessments to produce an overall measure of risk.

Key assumptions

- All UK cattle are given the CattleBCG vaccine.
  - WCS: Scotland and low risk areas in England and Wales are unlikely to vaccinate
- Data provided by the experimental work replicates what would be observed if CattleBCG was universally used as a vaccine in UK beef/dairy cattle farms.
- The survival of CattleBCG in different environments is similar to *M. bovis*.
- CattleBCG will not grow at any point within the processes used to produce the different products.
- Severely immuno-compromised people would consume unpasteurised milk/milk products or raw beef products.
  - WCS: Against medical advice
- The clinical symptoms of BCG disease caused by adverse reaction to child vaccination would be similar to the clinical symptoms that may occur through any foodborne exposure to BCG.

Consequence assessment

Consequence assessment

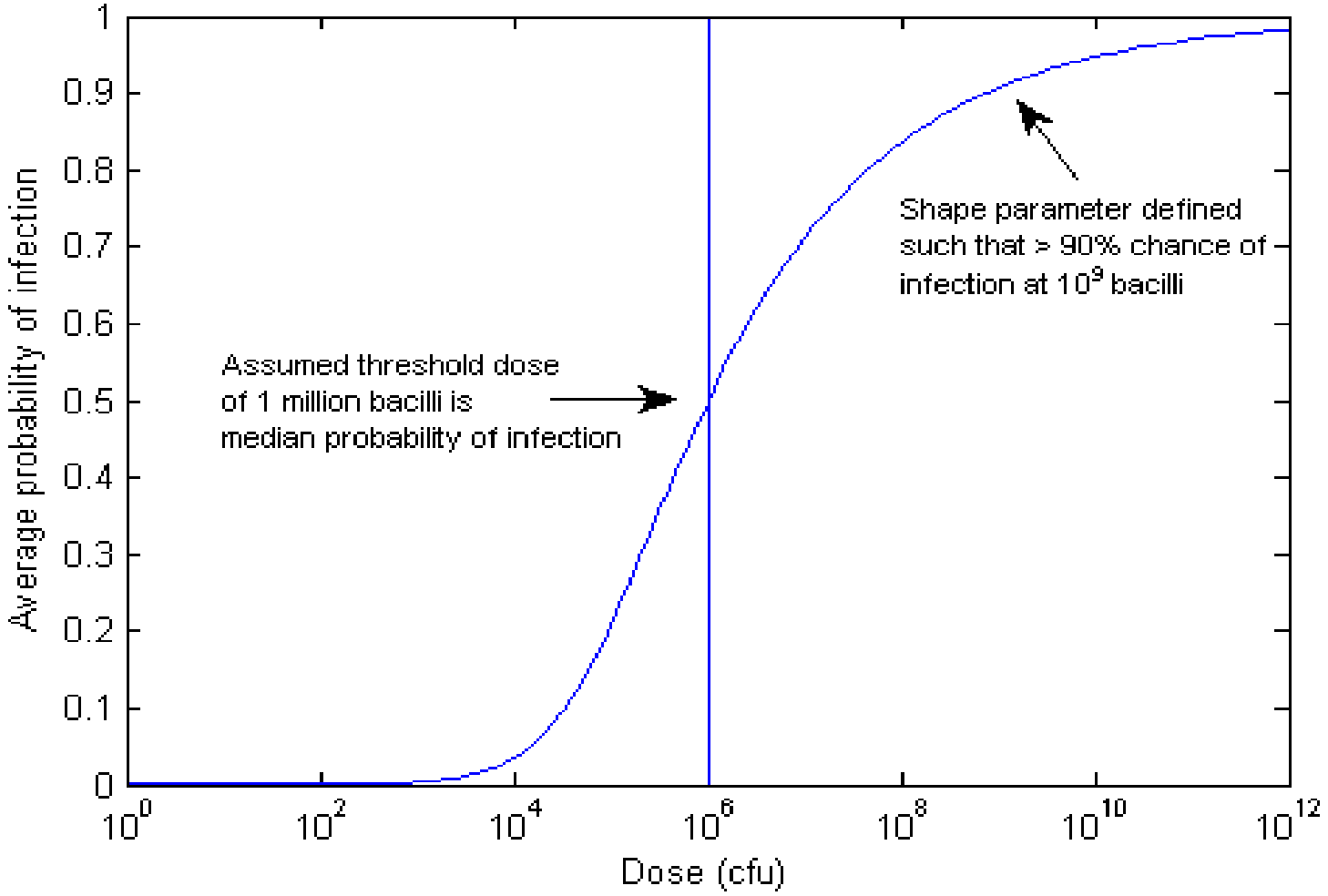
- Large uncertainty
  - Range of possible consequences due to infection with BCG.
  - Lack of knowledge on BCG ingested at low doses on both healthy and immuno-compromised populations.
  - Lack of information on the numbers of immuno-compromised people who would have increased susceptibility to BCG disease.
  - Lack of information for *M. bovis* via the gastrointestinal route.

- Probability of infection: Dose-response curve to describe probability of infection for a given dose.
- Probability of illness (given infected): Probability of regional BCG disease (10^{-3}) and disseminated BCG disease (5×10^{-6}).

Consequence assessment (probability of infection)

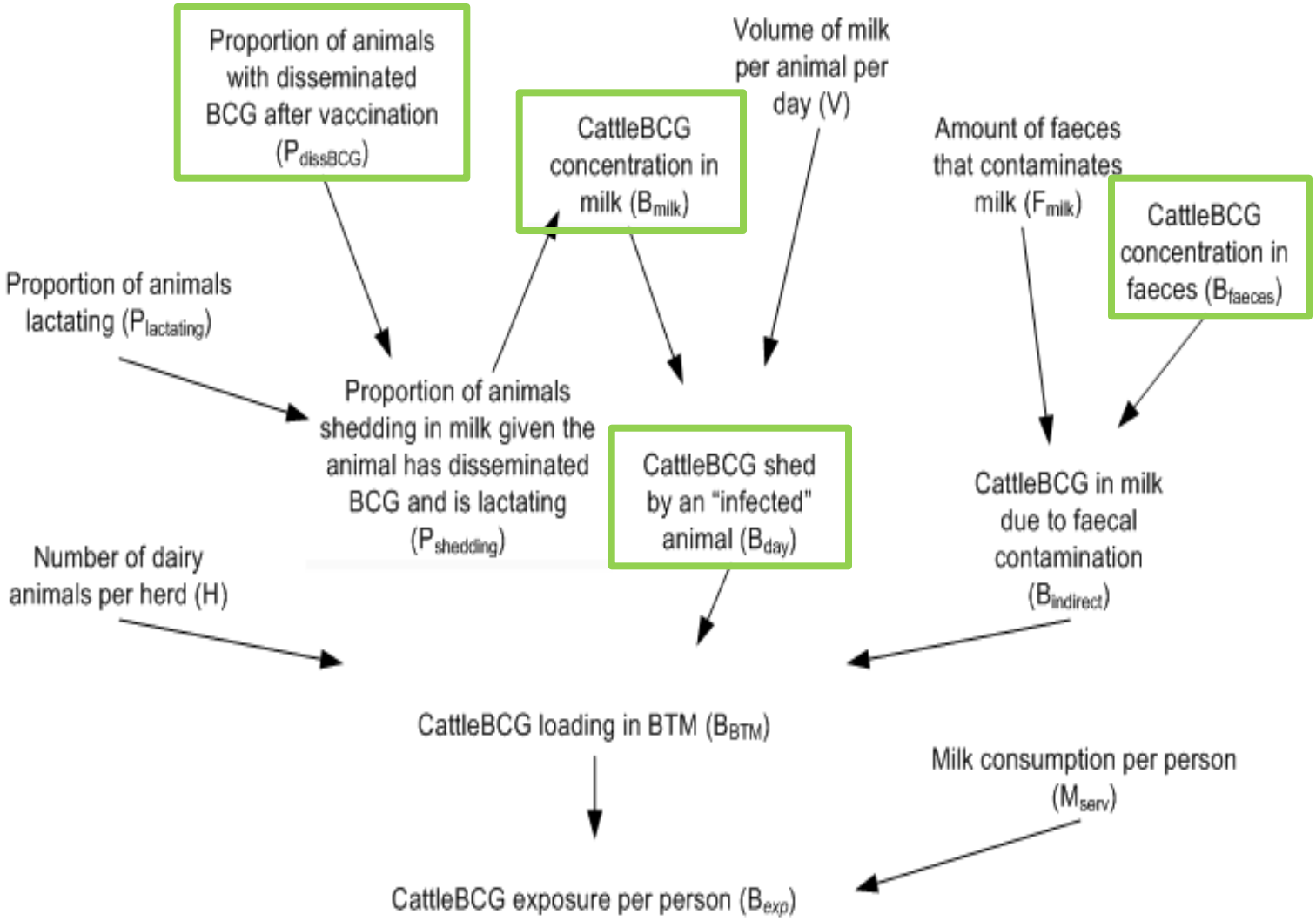
- Forms a key part of both dairy and beef risk assessment.
- Infectious dose of *M. bovis* thought to be millions of organisms (gastrointestinal route).
- CattleBCG less virulent than “wild-type” *M. bovis* – infectious dose of *M. bovis* inferred to be worst case.
- Original use of BCG via oral administration required much higher doses, e.g 10^7 - 10^9.

Dose-response curve



Milk and Milk Products Risk Assessment

Model framework: Raw milk



Raw milk: scenario analysis

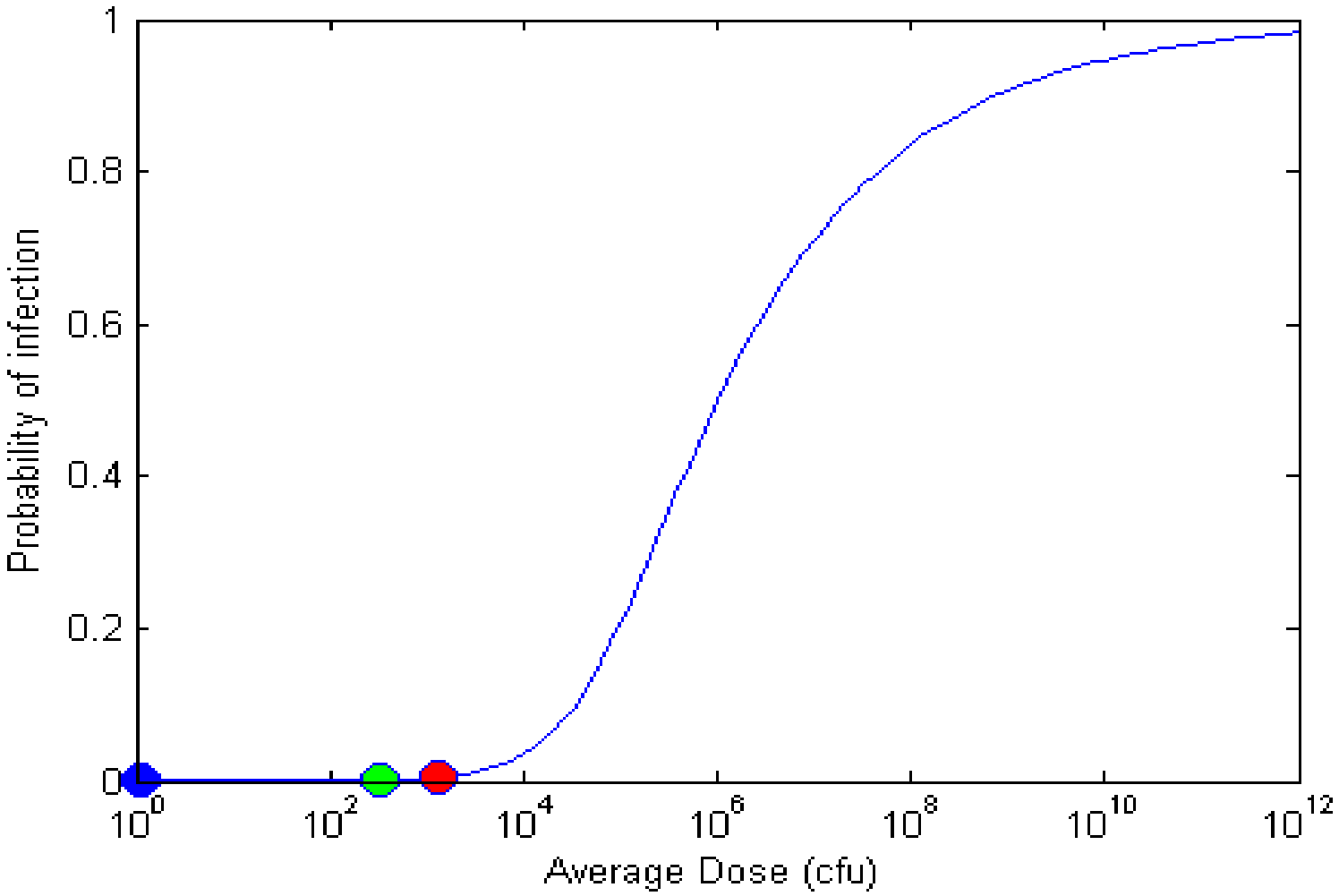
- Scenario 1 (Baseline)
  - Take results as reported. No BCG shedding in milk or faeces.
- Scenario 2
  - A proportion of cows have disseminated BCG, 0.03% of which are shedding BCG in milk at LoD. Also level of BCG in faeces in milk at LoD.
- Scenario 3
  - A proportion of cows have disseminated BCG, 100% of which are shedding BCG in milk at LoD. Also level of BCG in faeces in milk at LoD.
- Scenario 4
  - All cows have disseminated BCG and are shedding BCG in milk at LoD. Also level of BCG in faeces in milk at LoD.

Results: Milk & Milk Products

Outputs (per serving)	Scenario 1	Scenario 2	Scenario 3	Scenario 4
Exposure	0	0.153	341	1310
Probability of infection	0	5.97×10^{-7}	0.0013	0.0050
Probability of regional disease	0	5.97×10^{-10}	1.30×10^{-6}	5.00×10^{-6}
Probability of disseminated BCG disease	0	2.99×10^{-12}	6.50×10^{-9}	2.50×10^{-8}
Qualitative risk estimate (MILK)	Negligible	Negligible	Very Low (r) Negligible (d)	Very Low
Likelihood of scenario occurrence	High	Very low	Very Low	Negligible-Very Low

Qualitative risks (per serving) for pasteurised milk and raw milk cheese were *Negligible* for all scenarios.

CattleBCG exposure per serving (raw milk)



Beef Risk Assessment

Beef risk assessment

- Qualitative risk assessment with quantitative scenario analysis.
  - Minced meat from injection site tissue
  - <3 months post-vaccination; ≥ 3 months post-vaccination.

- Release assessment
  - What is the contamination level of edible tissue and organs with CattleBCG in cattle entering the slaughterhouse?
  - What is the sensitivity of detecting CattleBCG-positive animals/tissues via *post-mortem* meat inspection (PMMI)?
- Exposure assessment
  - Will CattleBCG survive the processing of the carcass, the preparation and consumption of beef products?
- Consequence assessment
  - What is the likely dose-response curve for humans for gastro-intestinal CattleBCG exposure? What are the clinical symptoms of illness? Are there any differences for immuno-compromised persons?

Beef: Scenario analysis

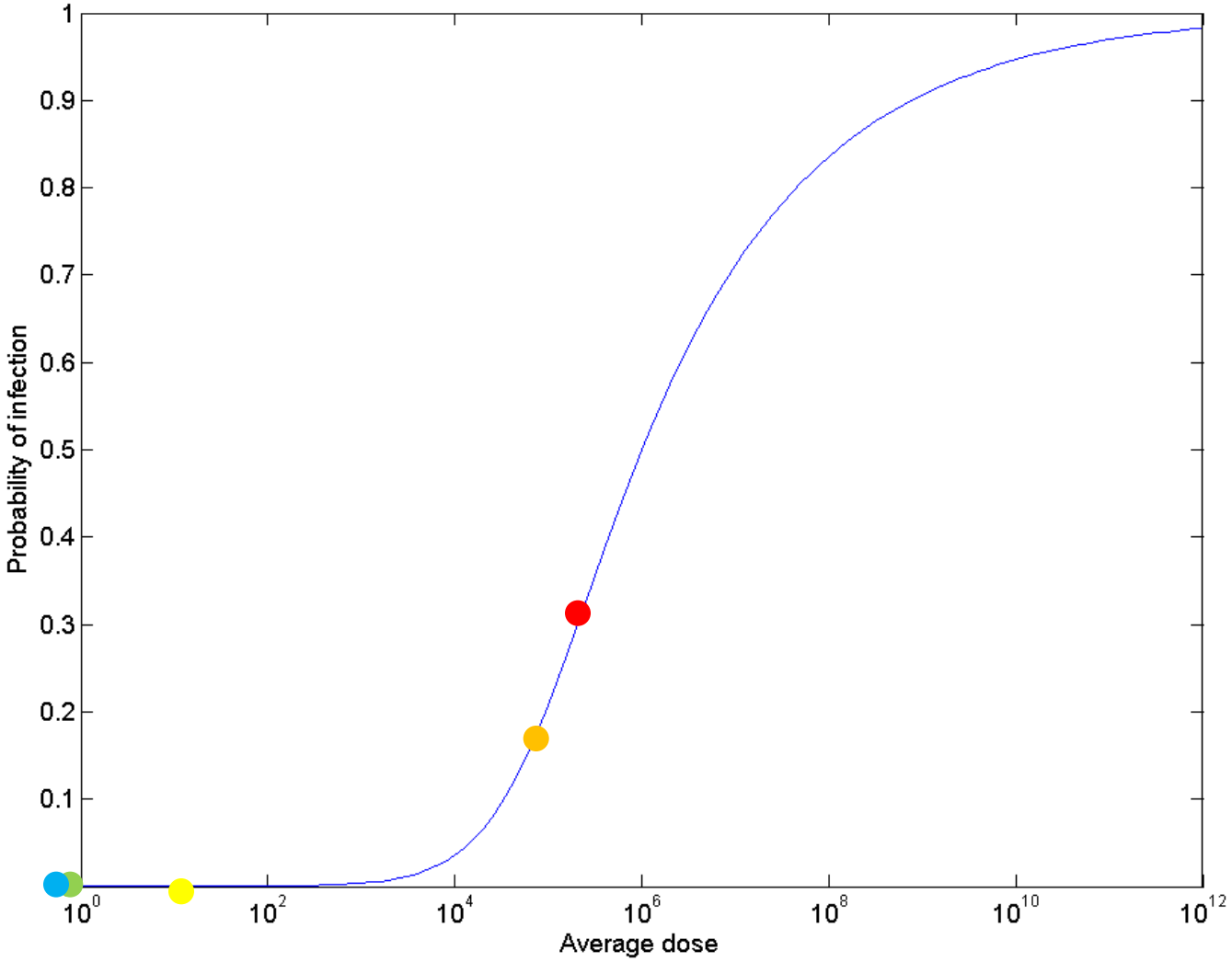
- **Scenario 1 (Baseline)**: Animals are slaughtered ≥3 months. Concentration of CattleBCG in meat is less than LoD. Burger cooked (rare). 16.6% injection site.
- **Scenario 2**: Animals are slaughtered ≥3 months. Concentration of CattleBCG in meat = LoD. Burger cooked (rare). 16.6% injection site.
- **Scenario 3**: Animals are slaughtered <3 months. Concentration of CattleBCG in meat = maximum observed. Burger cooked (rare). 16.6% injection site.
- **Scenario 4**: Animals are slaughtered <3 months. Concentration of CattleBCG in meat = maximum observed. Burger not cooked. 16.6% injection site.
- **Scenario 5 (absolute worst case)**: Animals are slaughtered <3 months. Concentration of CattleBCG in meat = maximum observed. Burger not cooked. 100% injection site.

Results: Beef products

Qualitative risk assessment	Risk of regional BCG disease	Risk of disseminated BCG disease
<3mths PI	Negligible/Very Low	Negligible
≥3mths PI	Negligible	Negligible

Scenario analysis	Exposure per serving	Risk of regional BCG disease per serving	Risk of disseminated BCG disease per serving	Qualitative risk (if scenario occurs)	Likelihood of scenario occurrence
Scenario 1	0.00	0.00	0.00	Negligible	Low-Medium
Scenario 2	0.06	$2.23*10^{-10}$	$2.23*10^{-13}$	Negligible	Low-Medium
Scenario 3	9	$3.63*10^{-8}$	$3.63*10^{-11}$	Negligible	Very Low
Scenario 4	93,106	$2.00*10^{-4}$	$2.00*10^{-7}$	Low (R) Very Low (D)	Negligible
Scenario 5	560,880	$4.3*10^{-4}$	$4.3*10^{-7}$	Low (R) Very Low (D)	Negligible

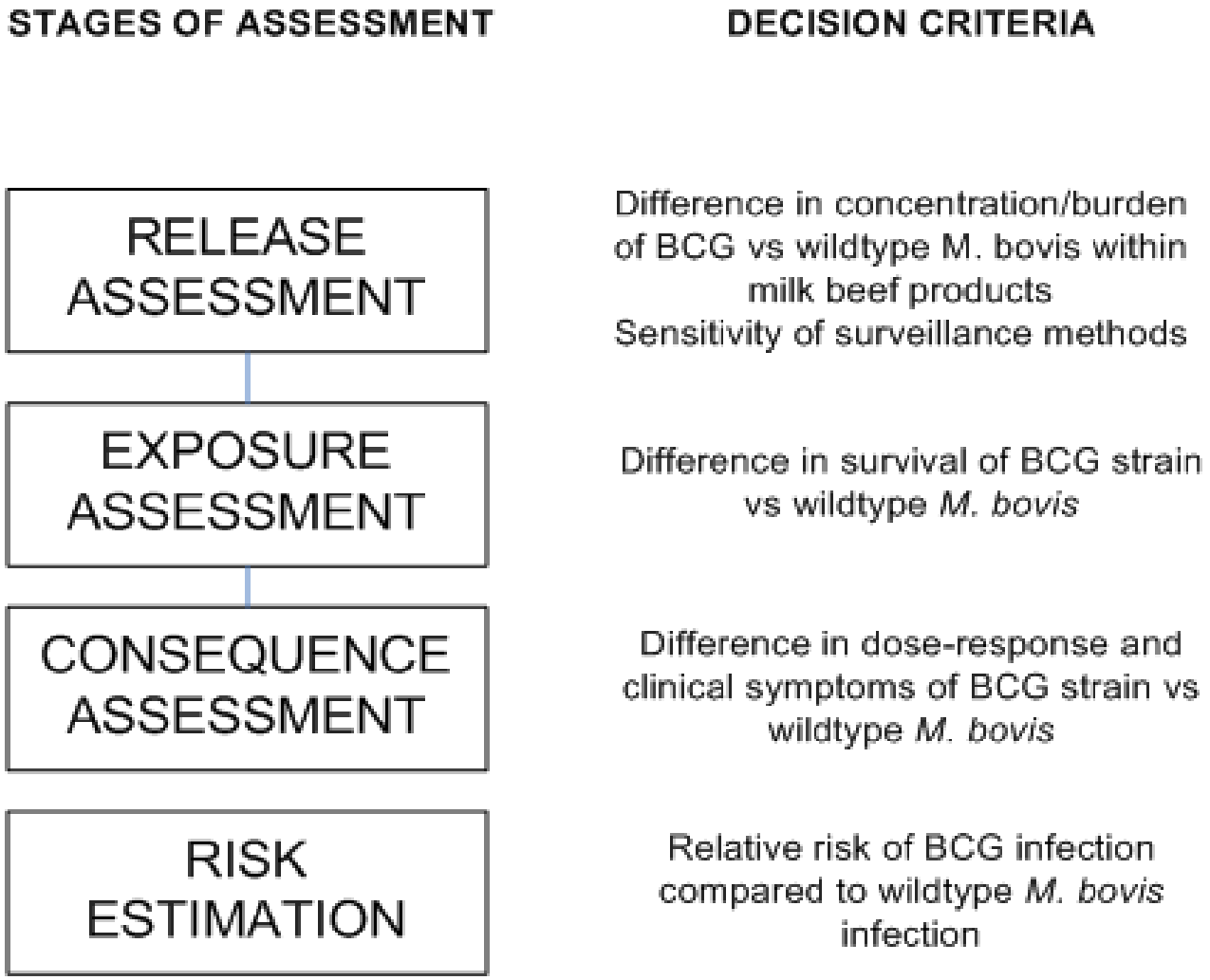
CattleBCG exposure per serving (Beef)



Comparison to ACMSF Risk Assessments

Comparison of CattleBCG to *M. bovis*

- Alternative approach is to compare risk of CattleBCG to *M. bovis.*
  - ACMSF RAs
- Risk pathways identical, although some key differences.



Results

- Key differences in the release assessment and dose-response.
  - Release assessment: more *M. bovis* in milk/tissue than CattleBCG
  - Consequence assessment: CattleBCG less likely to cause infection/illness than *M. bovis*.
- Raw Milk:
  - ACMSF concluded the risk to be V*ery Low*.
  - Estimate risk to be less than this (*Negligible*).
- Beef:
  - ACMSF concluded the risk to be *Very Low*.
  - Estimate risk to be less than this, particularly if slaughter ≥3 months post-vaccination.
    - *Negligible – Very Low (<3 months for regional disease)*.
    - *Negligible* (≥3 *months*)

Summary

Summary

- Quantitative assessments/scenarios carried out, where possible.
  - Many areas of data deficiencies.
- Baseline risk assessments
  - Risks (per serving) to the healthy population estimated to be *Negligible* via milk, milk products and beef.
  - Increased risks to immunocompromised population. *Negligible* – *Very Low* risks for regional BCG disease due to consumption of beef slaughtered <3 months post-vaccination.
- Scenario analyses
  - All risks assessed to be ≤ *Low*. However as scenario risks increase the likelihood of the scenario occurring decreases.
- Results are based on assumptions, many of which err on the side of caution.

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